Destruction of pancreatic β-cells by transgenic induction of PGE_2 in the islets.

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Type 2 diabetes mellitus is characterized by insulin resistance of peripheral tissues and dysfunction of pancreatic β-cells. Furthermore, the number of pancreatic β-cells decreases as a secondary effect of advanced type 2 diabetes, although molecular mechanism has not been elucidated. Recently, it has been shown that hyperglycemic conditions induce the expression of cyclooxygenase-2 (COX-2) in pancreatic islets and increase the downstream product prostaglandin E_2 (PGE_2). To investigate whether high glucose-induced PGE_2 has an adverse effect on pancreatic β-cells, we generated transgenic mice (*RIP-C2mE*) that express COX-2 and microsomal prostaglandin E synthase-1 (mPGES-1) in their β-cells using the rat insulin-2 gene promoter (RIP). The homozygous *RIP-C2mE* (*Tg/Tg*) mice showed severe hyperglycemia from 6 weeks of age. Although the heterozygous *RIP-C2mE* (*Tg/-*) mice showed normal blood glucose levels throughout their lifetime, this level increased significantly compared with that of wild-type mice when glucose was loaded. The relative number of β-cells to the total islet cell number was reduced to 54% and 14% in the *RIP-C2mE*(*Tg/-*) and (*Tg/Tg*) mice, respectively, whereas that in the wild-type mice was 84% (Fig. 1). Importantly, the proliferation rate in the islets of the *RIP-C2mE* (*Tg/Tg*) mice at four weeks of age decreased significantly in comparison to that in the wild-type mice. Because β-cells replicate not only during the postnatal period but also in the adult pancreas at a basal level, it is possible that increased PGE_2 signaling thus contributes to the reduction of the pancreatic β-cell mass through inhibition of proliferation, thereby aggravating diabetes further.

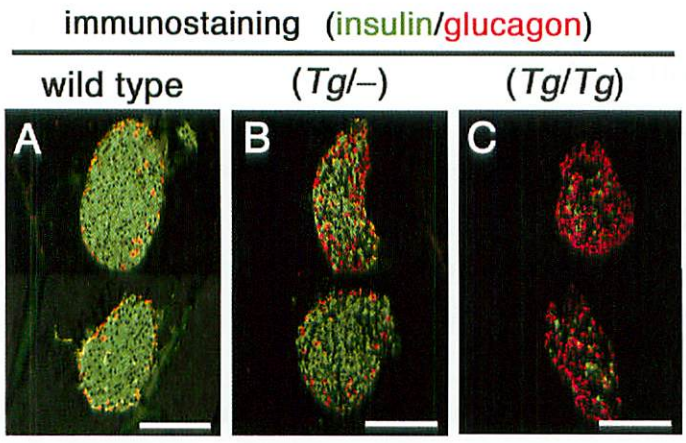

Fig. 1. Immunohistochemistry of insulin (*green*) and glucagons (*red*) to detect β-cells and α cells, respectively, in wild-type, heterozygous *RIP-C2mE*, and homozygous *RIP-C2mE* mice. Note significant decrease of β-cells in (*Tg/Tg*) mouse islets.

Reference: Oshima H, *et al.* J Biol Chem, 281: 29330, 2006.